

***IN THE UNITED STATES PATENT AND TRADEMARK OFFICE***

Applicant: Petr Dobrovolny  
Title: METHOD OF  
MANUFACTURING OF 7-  
ETHYL-10-  
HYDROXYCAMPTOTHECIN  
Appl. No.: 10/582,650  
International Filing Date: 12/14/2004  
371(c) Date: 6/13/06  
Examiner: Charanjit Aulakh  
Art Unit: 1625  
Confirmation Number: 1526

**DECLARATION OF PETR DOBROVOLNY UNDER 37 C.F.R. §1.131**

Dear Examiner Aulakh:

I, PETR DOBROVOLNY state and declare that:

1. I am the inventor of the invention recited in claims 23-37 of the patent application identified above. I made my invention while working in the Czech Republic.
2. Exhibit A is a copy of pages 72, 84, 88 and 89 from my research notebook, No. 768. My notebook entries on these pages are written in Czech. Exhibit B is an English translation of the four notebook pages. I have reviewed the translation and find that it accurately represents the content of my notebook entries. The pages describe the preparation of 7-ethyl-1,2,6,7-tetrahydrocamptothecin and 7-ethyl-10-hydroxycamptothecin according to methods that

are now the subject of claims 23-37. Exhibit C (C1-C4) shows HPLC Chromatograms for the compounds I synthesized, which are described by the notebook pages of Exhibit A.

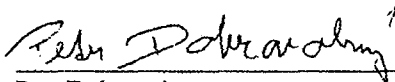
3. Page 88 of my notebook describes the procedure I used to hydrogenate 7-ethyl-camptothecin to provide 7-ethyl-1,2,6,7-tetrahydrocamptothecin. In the procedure, the equipment and amounts of reactant used were the same as that listed on pages 72 and 84, respectively, of the same notebook (also shown in Exhibit A). I used 5% platinum on carbon (0.022 equivalents of Pt with respect to starting material) in acetic acid (989 equivalents) and in the presence of a small amount of dimethylsulfoxide (0.28 equivalents). The hydrogenation was carried out with stirring (900 rpm) under hydrogen at a pressure of 5 atmospheres, at 65 °C for 43.5 hours. After the reaction was terminated, the catalyst was filtered off and washed with 10 ml acetic acid (141 equivalents), and the combined acetic acid solution used in the oxidation described on page 89 of my notebook. I submitted a sample of the hydrogenation product for analysis by high pressure liquid chromatography (HPLC). The resulting chromatogram of the hydrogenation product is shown in Exhibit C1. The product was compared to a reference standard and identified as 7-ethyl-1,2,6,7-tetrahydrocamptothecin, present as three diastereomers.

4. Page 89 of my notebook describes the procedure I used to oxidize 7-ethyl-1,2,6,7-tetrahydrocamptothecin to provide 7-ethyl-10-hydroxycamptothecin. The acetic acid solution (80 ml AcOH, 1130 equivalents) of 7-ethyl-1,2,6,7-tetrahydrocamptothecin from the hydrogenation described on page 88 was combined with 22 mL of water (983 equivalents) and iodobenzene diacetate (1.89 equivalents). The mixture was stirred for 15 minutes, concentrated, the residue mixed with acetonitrile and filtered. I submitted three samples from this experiment for HPLC analysis: oxidation reaction solution, the crystalline product and mother liquor. The resulting chromatograms of the samples are shown in Exhibits C2, C3, and C4, respectively. The crystalline product was identified as 7-ethyl-10-hydroxycamptothecin by comparison to a reference sample.

5. Although the dates of my notebook pages are redacted, the notebook pages are dated prior to May 12, 2003 and after the year 1995. In addition, the HPLC analysis shown in

Exhibit C were run prior to May 12, 2003 and after the year 1995. Collectively, Exhibits A, B and C show that I reduced to practice and invented the subject matter of claims 23-37 prior to May 12, 2003.

6. I hereby acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001) and may jeopardize the validity of the above-referenced application or any patent issuing thereon. All statements made of declarant's own knowledge are true and all statements made on information and belief are believed to be true.

  
Petr Dobrovolny

11.4.2008  
Date

## **EXHIBIT A**

## HYDROGENACE 7-ET-CPT

Návrada: 0,5 g 7-ET-CPT (768-65-1)  
 0,32 g 5% Pt/C (S. 05002 P1)  
 0,025 ml DMSO (S. 432316/1)  
 70 ml  $\text{CH}_3\text{COOH}$  (S. 20810)

Apparatura: Cítlkový autokláv,  $\text{N}_2$ ,  $\text{H}_2$ , kádinka,  
 váženka, tepl. válec, mikropipeta, sekovačka  
 s bučlivkou,

Postup: Do kádinky jsem nasázela 7-ET-CPT, do váženky  
 Pt/C a poté přidala do kádinky 2 ml  $\text{CH}_3\text{COOH}$   
 a dále do  $\text{H}_2$  zhomogenizováno. Poté jsem přidala DMSO,  
 promíchala a přivedla do autoklávu, zbytky  
 spláchnu zbytkem  $\text{CH}_3\text{COOH}$ .  
 Autokláv se zkompletoval, pustil se  $\text{N}_2$  (3x),  $\text{H}_2$  (3x) a  
 poté se pustil  $\text{H}_2$ . Otáčky minuty se zvýšily na 1000.

Hydrogenace začala v 10<sup>00</sup> hod při 50°C, v  
 10<sup>40</sup> hod 62°C, v 10<sup>52</sup> hod 64,2°C.

tlak 5 atm.  $\text{H}_2$ , minuty 1000 ot/min, t = 63-65°C

Teplota díky puštění chl. vody ubývá o 2°C méně, takže  
 se ve 12<sup>40</sup> h nastabila + na 67°C. Ve 12<sup>55</sup> h t = 64,9°C.

V 16 h zastavena hydrogenace. Filtrována  
 a promyta. Nymí a lednicí.

V lednici zfiltruji, teplou vodou rozpustím.

768-72-1

Odebrání vzorku na HPLC (2x):

N = 80 ml 7-ET-THCPT

# HYDROGENACE 7-ET-CPT

Návrada: 0,5g 7-ET-CPT (768-65-1)  
 0,32g 5% Pt/C (5. 05002 P1)  
 0,025 ml DMSO (5. 432316(1))  
 70 ml  $\text{CH}_3\text{COOH}$  (5. 20 810)

Aparatura: viz str 72

Postup: Do nádoby se umístí 7-ET-CPT, do nádoby Pt/C a pak se přidá k 7-ET-CPT. Zaleje se 1/2 celkové množství  $\text{CH}_3\text{COOH}$  a zhomogenizuje v UZ. \* Přelije do autoklávu a spóčítá 2 klythem ocetky. Aparatura se uzavře.

\* přidal se DMSO

Propláchno se  $\text{N}_2$  a  $\text{H}_2$ .

Hydrogenace spóčítána v 847h.

Plášť 900 ot/min, tlak 5 atm.  $\text{H}_2$

Vyhráto na 65°C v 950 hod.

V 940 hod = 61, 2°C

Konec hydrogenace v 950 hod. Hydrogenace 24 hod. (při 65°C)

v 10<sup>15</sup>h Filtrace a promytí  $\text{CH}_3\text{COOH}$  (5 ml). Něco prošlo nasele se znovu filtrout a propláchnout (spotřebo celkem asi 40 ml  $\text{CH}_3\text{COOH}$ )

768-84-1) N=124 mg 7-ET-THCPT. Vzorek HPLC: 64,94% 7-ET-THCPT, 7,97% 7-ET-THCPT (Světle oranžový až žlutý žlutý)

**PATR 1 84**  
**STR. 85**

Postup: V 1140h Nalito do 3hrdla banky (200 ml), přidalo se 35 ml oleminidy a dárkuje se IBDA: (tlášť se při 600 ot/min)

1. 0,613 g	v 1142h	žlutě oranžové	po 1/2 hod
2. 0,15 g	ve 12 <sup>12</sup> h	—	po 50 min
3. 0,13 g	ve 12 <sup>58</sup> h	— až hněd	po 30 min
4. 0,04 g	ve 13 <sup>27</sup> h	žlutě červenohněd	

# HYDROGENACE 7-ET-CPT

Nasada: viz str. 84

Aparatura: viz str. 72

Postup: Do kádinky jsem nasadila 7-ET-CPT a přidala Pt/C. Zcela čisti  $\text{CH}_3\text{COOH}$  a zhomogenizovala ve vz. Pridala draslík a po promíchání vložila do autoklávu. Vypuklím zrychlím do 60°C. Autokláv se uzavřel, po chvíli se uvolní, vyjměm a propíchnu  $\text{H}_2$  a  $\text{H}_2$ .

Hydrogenace začala v 13<sup>25</sup> hod.

Vytvářeno na 65°C ve 14<sup>00</sup> hod

Míchání 700 ot./min, tlak = 5 atm.  $\text{H}_2$ , teplota = 65°C.

Konec hydrogenace v 9<sup>30</sup> hod. Hydrogenace  
pri 65°C 43,5 hod.

768-88-7 / Ochlazeno na 25°C. Filtrace a promytí  $\text{CH}_3\text{COOH}$   
N= 80 ml 7-ET-THCPT. H<sup>2</sup>LC (30 ml): 65,80% 7-ET-THCPT. 8,23%  
zbytek při filtraci přechází na tuhou zbytku. 7-ET-CPT

Miloslav  
Dobránský

# PRŮPRAVA SN-38 z 7-ET-THCPT

Název: 80 ml 7-ET-THCPT (768-88-1)  
 22 ml dimethylu  
 0,77 g IBDA (s 4.7.3.79/1)  
 20 ml Acetonitrilu

Aparatura: Threda' 250 ml vana Buchi, p. VO,  
 elmag. míchání, odm. válec, vstředná,  
 buclivka s odsávací zkumavkou.

Postup: Do vany jímali dimethylu přisypali  
 1947 IBDA a hned zvlili 7-ET-THCPT. Během

Imaně zláta' přechází na světle červenou. 768-89-1  
 1949 Vzor na HPLC: 72,86% SN-38; 15,55% 7-ET-CPT

(60°C) Kuchl se 15 minut. Dřív na DVO odparit. Jdps. u se  
 160°C vod. Dostatečně to přehřívá. Konce 190°C  
 Na odparce nalit 10 ml Acetonitrilu, zhomogeni-  
 zováno na UZ. Docházíme štěr. vodou. Filtraci  
 a promyti 2x 10 ml Acetonitrilu.

768-89-2 N=0,2226 g SN-38. HPLC: 80,22% SN-38; 13,50% 7-ET-CPT  
 100%  $\Rightarrow$  0,586g (45,8% u'ložek na 7-ET-CPT)

768-89-3 Matečok - HPLC (3 $\mu$ l): 39,31% SN-38; 28,2% 7-ET-CPT

Mohelná  
 Dobrávová

## VÝPOČET MNOŽSTVÍ VODY DO 7-ET-THCPT:

Objem 7-ET-THCPT \* 0,282 = x ml dimethylu



## **EXHIBIT B**

## HYDROGENATION OF 7-Et-CPT

	<p><u>Charge:</u> 0.5g 7-Et-CPT (768-65-1)  0.32g 5% Pt/C (batch no. 05002 PI)  0.025 mL DMSO (batch no. 432316/1)  70 mL CH<sub>3</sub>COOH (batch no. 20810)</p> <p>Equipment: 0.5L metal autoclave, N<sub>2</sub>, H<sub>2</sub>, a beaker, a weighing bottle, a graduated cylinder, a micropipette, büchner filter with vacuum pump</p> <p>Procedure: 7-Et-CPT was weighed to a beaker, Pt/C was weighed to a weighing bottle and then it was added to the beaker, it was poured with a part of CH<sub>3</sub>COOH and homogenized on US. Then DMSO was added, stirred and transferred to an autoclave. The residues were washed with the remaining CH<sub>3</sub>COOH.</p> <p>The autoclave was completed and switched on 500 rpm. The autoclave was washed with N<sub>2</sub> (3x) and H<sub>2</sub> (3x) and then H<sub>2</sub> was switched on. Revolutions were increased to 1000 rpm.</p> <p>Hydrogenation started at 10 am at 50°C, at 10:40 am - 62°C, at 10:52 am - 64.2°C</p> <p>Pressure of H<sub>2</sub> - 5 atm, 1000 rpm, t - 63 - 65°C</p> <p>Thanks to the cooling water, the temperature shows 2°C less, so at 12:40 am the temperature was set to 67°C. At 12:55 am t = 64.9°C</p> <p>The hydrogenation was stopped at 4 pm. Filtered and washed. Now in the fridge.</p>
<p>768-72-1</p> <p>768-73-1 100% yield → 0.0505g</p> <p>768-73-2</p>	<p>The suspension solidified in the fridge, it was dissolved in hot water. A sample was taken for HPLC.</p> <p>N about 80 mL 7-Et-THCPT</p> <p>&lt;page 72 ends, page 73 begins&gt;</p> <p>Thickened on RVO to an oily consistence. 8 mL of MeOH was added. Crystals were released. Filtration &amp; washing with 10 ml of MeOH. Drying at 35°C in a drier.</p> <p>N = 0.2385 g 7-Et-CPT. HPLC: 94.50 7-Et-CPT</p> <p>mother liquor HPLC: (20µL): 58.69% 7-Et-THCPT</p> <p style="text-align: right;">Illegible signature  <span style="display: inline-block; width: 100px; height: 1.2em; background-color: black; vertical-align: middle;"></span> Legible signature - Dobrovolný</p>

## HYDROGENATION OF 7-Et-CPT

	<p><u>Charge:</u> 0.5g 7-Et-CPT (768-65-1) 0.32g 5% Pt/C (batch no. 05002 PI) 0.025 mL DMSO (batch no. 432316/1) 70 mL CH<sub>3</sub>COOH (batch no. 20810)</p> <p>Equipment: see page 72</p> <p>Procedure: 7-Et-CPT was weighed to a beaker, Pt/C was weighed to a weighing bottle and then it was added to the beaker, it was poured with a half of the total quantity of CH<sub>3</sub>COOH and homogenized on US. DMSO was added. Then it was transferred to an autoclave. The residues were washed with the remaining CH<sub>3</sub>COOH. The autoclave was closed and washed with N<sub>2</sub> and H<sub>2</sub>.</p> <p>Hydrogenation started at 8:47 am. 900 rpm, pressure of H<sub>2</sub> – 5 atm, heated to 65°C at 9:50 am</p> <p>At 9:10 am = 61.2°C</p>																
	<p>End of hydrogenation at 9:50 am. The hydrogenation lasted for 24 hours (at 65°C).</p> <p>At 10:45 am filtration and washing with CH<sub>3</sub>COOH (5 mL). Something went through, new filtration and washing were necessary (total consumption of about 40 mL of CH<sub>3</sub>COOH).</p>																
768-84-1	<p>N=124 mL 7-Et-THCPT. Sample HPLC: 64.94% 7-Et-THCPT, 7.975 7-Et-CPT (light orange to dark yellow solution)</p>																
	<p>Procedure: At 11:40 am it was poured to a 250 mL 3-neck flask, 35 mL of demiwater was added and IBDA was dosed (stirred with 600 rpm)</p> <table><tr><td>1. 0.613g</td><td>at 11:42 am</td><td>dark orange</td><td>after 30 minutes</td></tr><tr><td>2. 0.15g</td><td>at 12:12 am</td><td>dark orange</td><td>after 50 minutes</td></tr><tr><td>3. 0.13g</td><td>at 12:55 am</td><td>dark orange to brown</td><td>after 30 minutes</td></tr><tr><td>4. 0.04g</td><td>at 1:27 pm</td><td>dark reddish brown</td><td></td></tr></table>	1. 0.613g	at 11:42 am	dark orange	after 30 minutes	2. 0.15g	at 12:12 am	dark orange	after 50 minutes	3. 0.13g	at 12:55 am	dark orange to brown	after 30 minutes	4. 0.04g	at 1:27 pm	dark reddish brown	
1. 0.613g	at 11:42 am	dark orange	after 30 minutes														
2. 0.15g	at 12:12 am	dark orange	after 50 minutes														
3. 0.13g	at 12:55 am	dark orange to brown	after 30 minutes														
4. 0.04g	at 1:27 pm	dark reddish brown															

## HYDROGENATION OF 7-Et-CPT

	<p><u>Charge:</u> see page 84</p> <p>Equipment: see page 72</p> <p>Procedure: 7-Et-CPT was weighed to a beaker, Pt/C was added to the beaker, it was poured with a part of CH<sub>3</sub>COOH and homogenized on US. DMSO was added. Then it was stirred and transferred to an autoclave. The residues were washed with the remaining CH<sub>3</sub>COOH.</p> <p>The autoclave was closed, stirring and heating was switched on and it was washed with N<sub>2</sub> and H<sub>2</sub>.</p> <p>Hydrogenation started at 1:25 pm. 900 rpm, pressure of H<sub>2</sub> – 5 atm, heated to 65°C at 2:00 pm</p>
768-88-1	<p>End of hydrogenation at 9:30 am. The hydrogenation lasted for 43.5 hours (at 65°C).</p> <p>Cooled to 25°C. Filtration and washing with CH<sub>3</sub>COOH</p> <p>N=80 mL 7-Et-THCPT. HPLC (30μL): 65.80% 7-Et-THCPT 8.23% 7-Et-CPT The light yellow solution at the filtration turns to a dark yellow solution.</p> <p style="text-align: right;"><i>Illegible signature</i></p> <p style="text-align: right;">[redacted] <i>Legible signature - Dobrovolný</i></p>

## 89

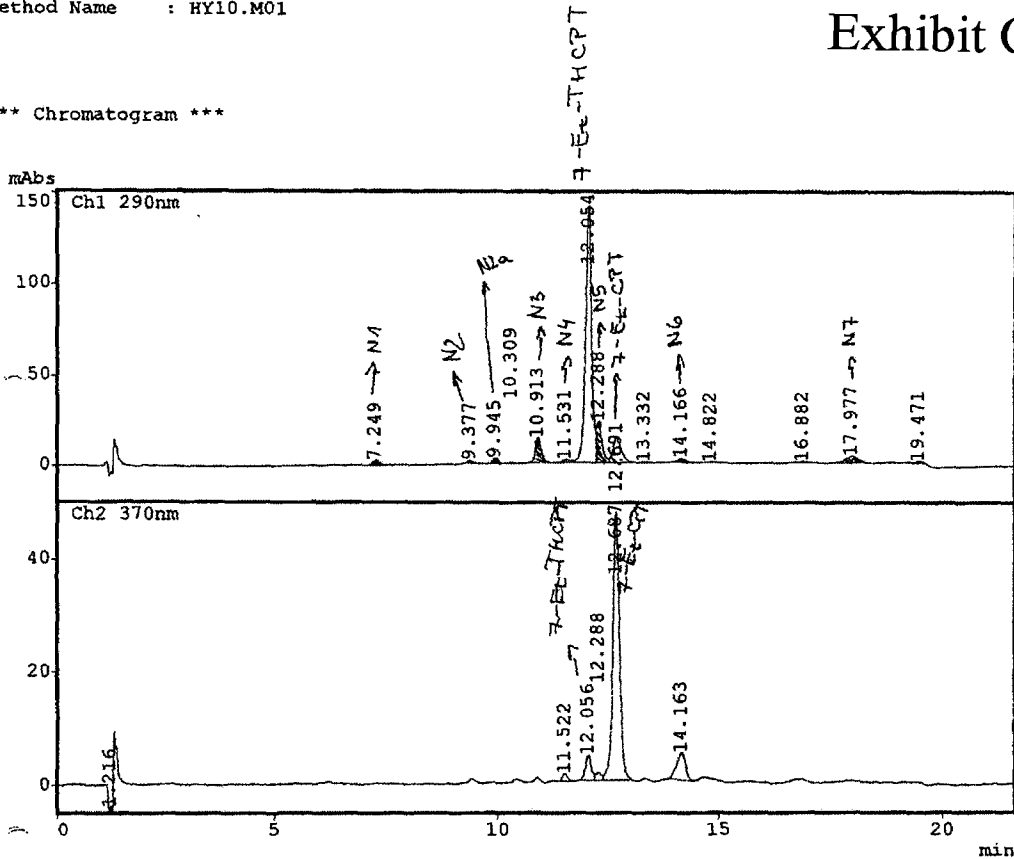
<div data-bbox="214 296 355 329" style="background-color: black; width: 115px; height: 30px; margin-bottom: 10px;"></div> <div data-bbox="214 739 362 842">768-89-1 (60°C) RVO=1Hr</div> <div data-bbox="214 921 397 1014">768-89-2 100%yield→ 0.486g 768-89-3</div>	<div data-bbox="410 329 963 478"><u>Charge:</u> 80 mL 7-Et-THCPT (768-88-1) 22 mL demiwater 0.77g IBDA (batch no. 417379/1) 20 mL acetonitrile</div> <div data-bbox="410 512 1416 592"><u>Equipment:</u> a 250-mL 1-neck Büchi beaker, RVO, an elmag. stirrer, a graduated cylinder, a weighing bottle, a büchner filter with vacuum pump</div> <div data-bbox="410 625 1416 728"><u>Procedure:</u> Demiwater was poured to a flask, IBDA was added and it was poured with 7-Et-THCPT immediately. The dark yellow color turns to light reddish brown.</div> <div data-bbox="410 728 1416 911">At 9:49 am a sample was taken for HPLC: 72.86% SN-38, 15.55% 7-Et-CPT Stirred for 15 min. Then evaporation on RVO till 10:00 am. End at 11:10 am. 10 mL of acetonitrile poured on the evaporation residue, homogenized on US. Cooled with cold water. Filtration and washing with about 10 mL of acetonitrile.</div> <div data-bbox="410 911 1243 1024">N=0.2226g SN-38. HPLC: 80.22% SN-38; 13.50% 7-Et-CPT (45.8% yield to 7-Et-CPT) Mother liquor HPLC (30µL): 39.31% SN-38; 25.82% 7-Et-CPT</div> <div data-bbox="1170 1207 1416 1241"><i>Illegible signature</i></div> <div data-bbox="863 1276 1416 1320"><div data-bbox="863 1276 998 1320" style="background-color: black; width: 110px; height: 40px; display: inline-block;"></div><i>Legible signature – Dobrovolný</i></div> <div data-bbox="410 1356 1243 1423">CALCULATION OF WATER QUANTITY FOR 7-ET-THCPT 7-Et-THCPT volume x 0.282 – x mL demiH<sub>2</sub>O</div>
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## **EXHIBIT C**

CLASS-LC10 Ver.=1.64A SYS=1 REPORT.NO=8 DATA=HY10.K01 10:04:28  
Vial # : 90  
Sample : 7-Et-THCPT  
ID : 768-88-1  
Inj. Volume : 10  
Type : Unknown  
Detector : SPD-M10A  
Operator : Buchta  
Method Name : HY10.M01

# Exhibit C1

\*\*\* Chromatogram \*\*\*



\*\*\* Peak Report \*\*\*

PKNO	ChNO	TIME	AREA	CONC	NAME	HEIGHT
1	2	1.216	1185			818
2	1	7.249	26142	1.2689		2752 N1
3	1	9.377	14333	0.6958		1786 N2
4	1	9.945	22365	1.0856		2891 N2 a
5	1	10.309	4577	0.2222		544
6	1	10.913	127527	6.1903		13910 N3
7	1	11.531	20869	1.0130		1486 N4
8	2	11.522	10840			1323
8	1	12.054	1355610	65.8024	7-Et-THCPT	140795
9	2	*12.056	40532			4375
9	1	12.288	196504	9.5385		22707 N5
10	2	12.288	13172			1479
10	1	12.691	169592	8.2321	7-Et-CPT	13461
11	2	*12.687	500452			47687
11	1	13.332	4884	0.2371		474
12	1	14.166	22919	1.1125		2061 N6
13	2	14.163	64983			4773
14	1	14.822	2725	0.1323		248
15	1	16.882	10049	0.4878		733
15	1	17.977	67269	3.2653		3621 N7
16	1	19.471	14759	0.7164		1064

<Temporary>

8 - 1/2

2691287

100.0000

268988

<Temporary>

8 - 2/2

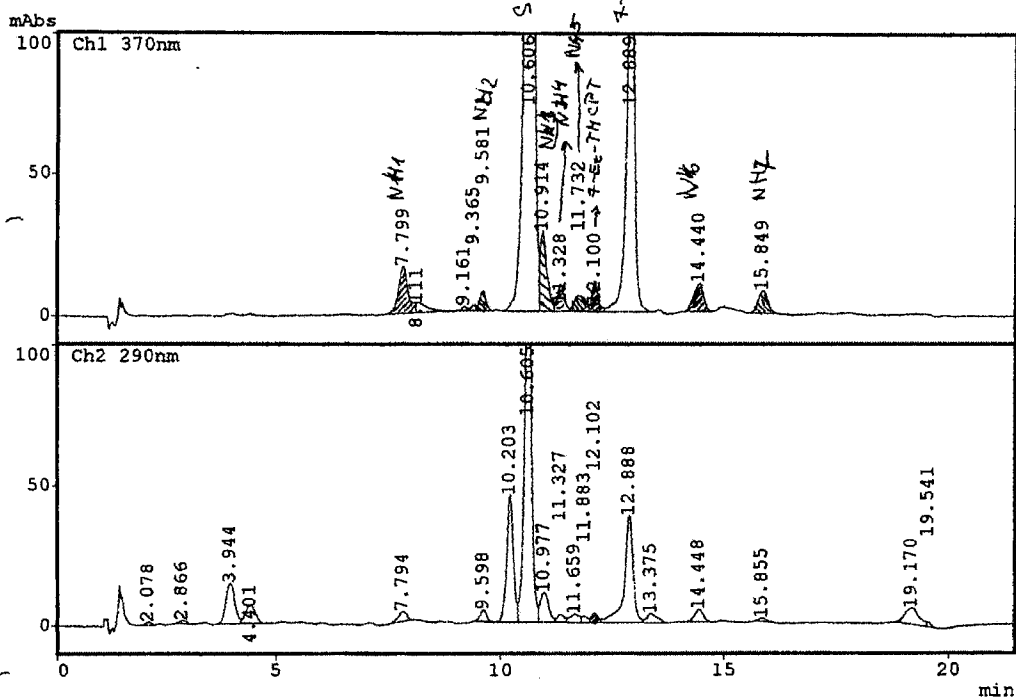




ID : 768-89-1  
 Inj. Volume : 25  
 Type : Unknown  
 Detector : SPD-M10A  
 Operator : Buchta  
 Method Name : HY12.M01

# Exhibit C2

\*\*\* Chromatogram \*\*\*



\*\*\* Peak Report \*\*\*

PKNO	ChNO	TIME	AREA	CONC	NAME	HEIGHT
1	2	2.078	9358			1094
2	2	2.866	12736			1192
3	2	3.944	203759			14350
4	2	4.401	100667			6579
5	1	7.799	237360	2.2196		16259 NH1
6	1	7.794	45972			3580
7	1	8.111	64349	0.6017		3603
8	1	9.161	11592	0.1084		1492
9	1	9.365	15867	0.1484		1840
10	1	9.581	62022	0.5800		6646 NH2
11	2	9.598	39517			4055
12	2	10.203	459287			45696
13	1	10.606	7791901	72.8629		821960 SN-38
14	2	10.605	1704891			182583
15	1	10.914	295566	2.7639		28025 NH4
16	2	10.977	140194			10367
17	1	11.328	96857	0.9057		9138 NH4
18	2	11.327	29673			2756
19	2	11.659	41715			2799
20	1	11.732	96183	0.8994		5265 NH5
21	2	11.883	21211			2187

<Temporary>

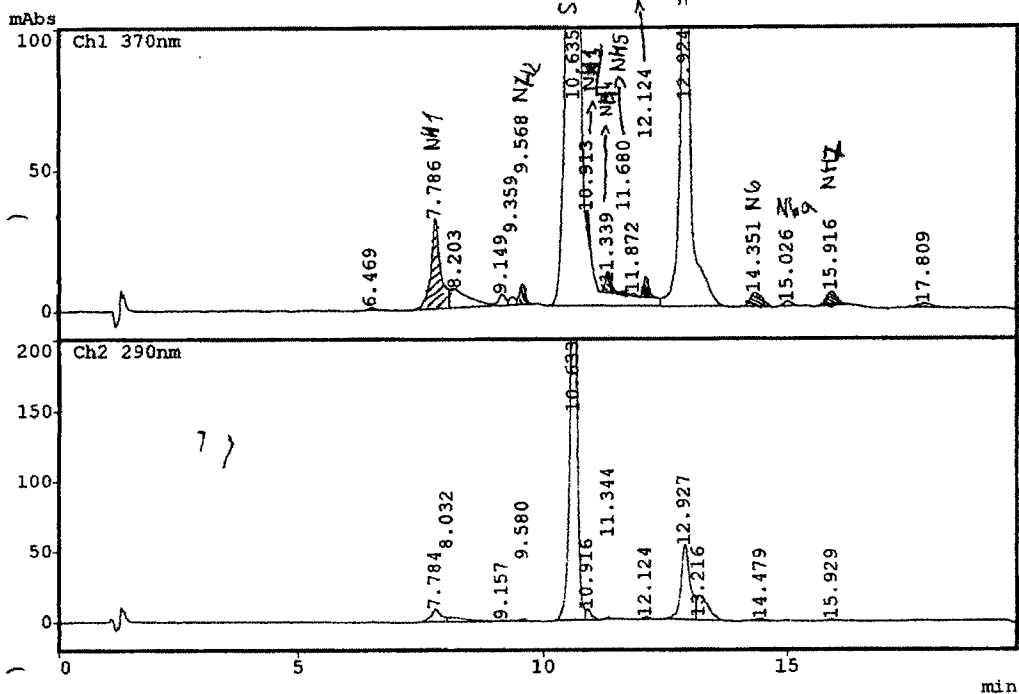
18	1	12.100	101379	0.9480	10547	7-Et-THCPT
	2	12.102	32123		3428	
19	1	12.889	1662846	15.5494	143661	7-Et-CPT
	2	12.888	519494		38394	
20	2	13.375	50151		3144	
21	1	14.440	143330	1.3403	9622	N46
	2	14.448	57551		4477	
22	1	15.849	114677	1.0724	7642	NH2
	2	15.855	13725		1135	
23	2	19.170	125623		5800	
24	2	19.541	11300		1704	
			14312873	100.0000	1401014	

Temporary>

Sample : 768-89-2  
 ID : 768-89-2  
 Inj. Volume : 10  
 Type : Unknown  
 Detector : SPD-M10A  
 Operator : Buchta  
 Method Name : HY14.M01

mdsda 0.5g 7-Et-CPT  
 in 70 ml CH<sub>3</sub>COOH  
 Hyd. 43,5h  
**Exhibit C3**

\*\*\* Chromatogram \*\*\*



\*\*\* Peak Report \*\*\*

PKNO	ChNO	TIME	AREA	CONC	NAME	HEIGHT
1	1	6.469	9579	0.0541		904
2	1	7.786	432200	2.4426	NH1	31618
2	1	7.784	131802			8861
3	2	8.032	81311			3198
4	1	8.203	176380	0.9968		6575
5	1	9.149	43366	0.2451		4058
6	2	9.157	4938			688
7	1	9.359	26772	0.1513		2978
7	1	9.568	60383	0.3413	NH2	7157
8	2	9.580	10834			1516
8	1	10.635	14195023	80.2254	SN-38	1393882
9	2	10.633	3133537			336897
9	1	10.913	28174	0.1592	NH3	5360
10	2	10.916	58573			7512
10	1	11.339	60351	0.3411	NH4	7228
11	2	11.344	11393			1585
11	1	11.680	15699	0.0887	NH5	1299
12	1	11.872	6722	0.0380		1038
13	1	12.124	58092	0.3283	7-Et-THCPT	7056
14	2	12.124	16064			2007
14	1	12.924	2388151	13.4970	7-Et-CPT	186473

<Temporary>

	2	12.927	699268		53199	
15	2	13.216	299481		17251	
16	1	<u>14.357</u>	81994	<u>10.4634</u>	<u>74893</u>	NK6
17	2	14.479	22986		1413	
18	1	<u>15.026</u>	17401	<u>0.0983</u>	1597	NH6a
19	1	<u>15.916</u>	70242	<u>0.3970</u>	<u>4923</u>	NH7
	2	15.929	13901		1104	
20	1	17.809	23403	0.1323	1276	
-----						
			22178019	100.0000	2103543	

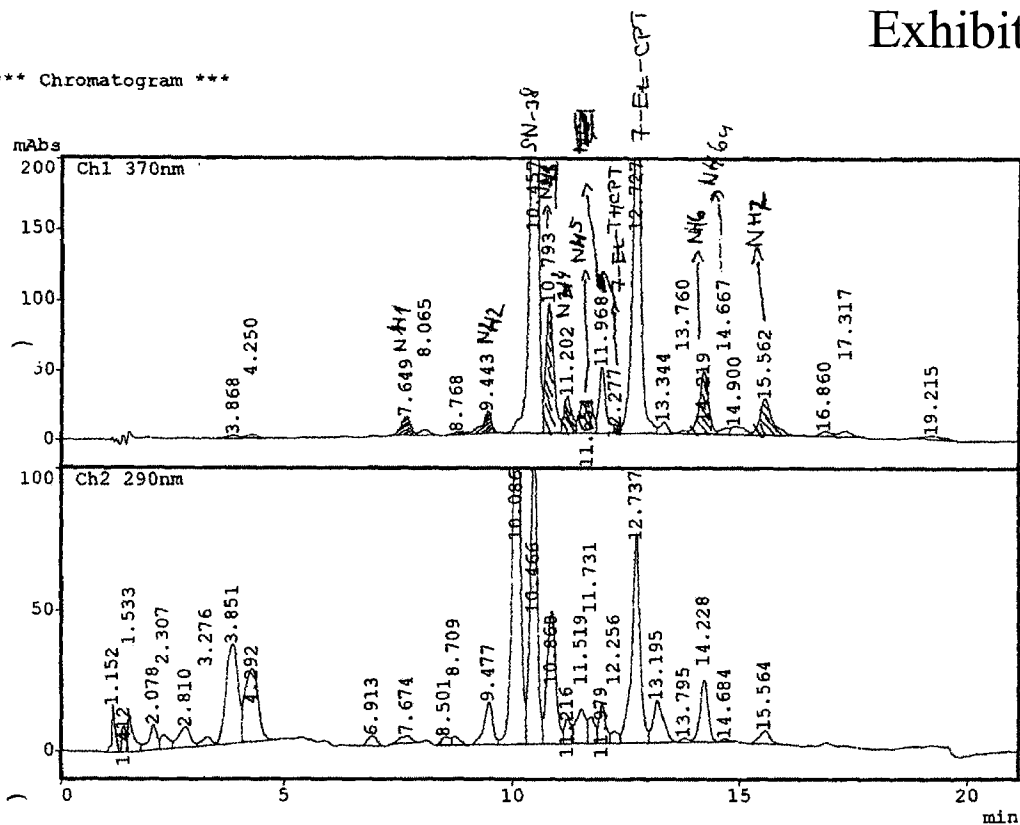
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Vial # : 11  
 Sample : SN-38-filtrat  
 ID : 768-89-3  
 Inj. Volume : 35  
 Type : Unknown  
 Detector : SPD-M10A  
 Operator : Buchta  
 Method Name : HY15.M01

## Exhibit C4

\*\*\* Chromatogram \*\*\*



\*\*\* Peak Report \*\*\*

PKNO	ChNO	TIME	AREA	CONC	NAME	HEIGHT
1	2	1.152	89088			16787
2	2	1.412	58743			9019
3	2	1.533	110664			13153
4	2	2.078	114356			8950
5	2	2.307	71341			5141
6	2	2.810	132876			7000
7	2	3.276	42249			3022
8	1	3.868	36847	0.2748		2222
9	2	3.851	658300			35348
10	1	4.250	42287	0.3154		2309
11	2	4.292	521477			25944
12	1	6.913	47289			3508
13	1	7.649	192377	1.4348	NA1	13300
14	2	7.674	47005			2696
15	1	8.065	60921	0.4544		4274
16	2	8.501	35963			2624
17	2	8.709	30255			2885
18	1	8.768	37335	0.2785		1887
19	1	9.443	227410	1.6961	NH2	15624
20	2	9.477	210773			15100
21	2	10.086	1934972			174271

21	1	10.457	5270514	39.3098	490915	SN-38
	2	10.466	1151863		109897	
22	1	10.793	1101620	8.2164	92234	NH4
23	2	10.868	643056		47453	
24	1	11.202	321031	2.3944	26508	NH4
	2	11.216	96591		8851	
25	2	11.519	180752		12164	
26	1	11.654	462099	3.4465	22140	NH5
27	2	11.731	102865		9400	
28	1	11.968	494503	3.6882	47816	WCH
	2	11.979	141488		13985	
29	2	12.256	51904		4249	
30	1	12.277	47916	0.3574	6080	7-Et-THCPT
31	1	12.727	3462306	25.8234	283837	7-Et-CPT
	2	12.737	978650		74416	
32	2	13.195	242877		15130	
33	1	13.344	102000	0.7608	7981	
34	1	13.760	27968	0.2086	2282	
35	2	13.795	20045		1626	
36	1	14.219	627090	4.6771	45020	NH6
	2	14.228	273081		21953	
37	1	14.667	61565	0.4592	4472	NH6a
	2	14.684	11515		1224	
38	1	14.900	122053	0.9103	5738	
39	1	15.562	494479	3.6880	25981	NH2
	2	15.564	73277		4520	
40	1	16.860	59809	0.4461	3599	
41	1	17.317	78253	0.5836	4139	
42	1	19.215	77255	0.5762	2634	
21480951				100.0000	1761376	